



Exenatide-Induced Acute Renal Failure: A Case Report

Eksenatide İlişkili Akut Böbrek Yetmezliği: Olgu Sunumu

Mustafa Ünübol, Fatih Gencer*, Hakan Akdam**, Yavuz Yeniçerioglu**, Harun Akar**, Engin Güney

Adnan Menderes University Medical Faculty, Division of Endocrinology and Metabolism, Aydın, Turkey

*Adnan Menderes University Medical Faculty, Department of Internal Medicine, Aydın, Turkey

**Adnan Menderes University Medical Faculty, Division of Nephrology, Aydın, Turkey

Abstract

Exenatide is a glucagon-like peptide-1 receptor agonist that is commonly used in the treatment of type II diabetes mellitus for its effects on the incretin system. The use of exenatide is also related to weight loss and it has reportedly been known to induce acute renal failure (ARF) according to clinical reports. We observed ARF and severe weight loss two months after beginning the treatment with exenatide in a 59-year-old female patient with type II diabetes mellitus. We present this case in which ARF was considered to be a rare adverse effect of exenatide use. In conclusion, renal functions should be closely monitored, especially in patients prescribed nephrotoxic agents and for those with a high risk of nephropathy and dehydration due to their treatment with exenatide. The usage of this drug should also be carefully planned in these patients. *Turk Jem 2013; 17: 68-70*

Key words: Exenatide, acute renal failure, obesity, diabetes

Özet

Eksenatide, inkretin sistem üzerine etkileriyle Tip 2 DM tedavisinde sık kullanılan bir ajan olup glucagon benzeri peptid-1 (GLP-1) reseptörü agonistidir. Eksenatide kullanımı kilo kaybı ile ilişkilidir ve akut böbrek yetmezliğine (ABY) neden olduğu klinik raporlar şeklinde bildirilmiştir. Elli dokuz yaşında Tip 2 DM tanılı bayan hastada eksenatide tedavisinden 2 ay sonra ciddi kilo kaybı ve ABY gözlemledik. Biz, eksenatide kullanımı sonrası gelişen nadir bir advers olay olarak ABY gelişmesi nedeniyle olguyu sunduk. Sonuç olarak, nefrotoksik ajan kullanan, nefropati riski yüksek olan ve dehidratasyon riski oluşturabileceği öngörülen hastalarda eksenatide'nin dikkatli kullanılması ve bu hastalarda böbrek fonksiyonlarının yakın takip edilmesi gerektiğini vurgulamak istemekteyiz. *Turk Jem 2013; 17: 68-70*

Anahtar kelimeler: Eksenatide, akut böbrek yetmezliği, obezite, diyabet

Introduction

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist that is commonly used in the treatment of type II diabetes mellitus (DM) for its effect on the incretin system (1). The most prevalent adverse reactions associated with this treatment are nausea and vomiting, but their intensity and frequency slowly diminish and disappear (2). In addition, the use of exenatide is also related to weight loss (3), and it has reportedly been known to induce acute renal failure (ARF) according to clinical reports (4-6). However, in a retrospective study, no significant relationship was found between exenatide use and

ARF (7). We observed ARF and severe weight loss two months after beginning treatment with exenatide in a 59-year-old female patient with type II DM, therefore, we present this case in which ARF was considered to be a rare adverse effect of exenatide use.

Case Report

A 59-year-old obese female patient had been diagnosed with type II DM 15 years previously, and she was taking metformin (1 g 2x1/day), sitagliptin (100 mg/day), and nateglinide (120 mg 3x1/day). Her weight had increased to 100 kilograms (kg) in the last year from

a previous weight of 86 kg. Her medical records revealed a prior diagnosis of hypertension from 10 years earlier, which necessitated the use of candesartan (16mg + hydrochlorothiazide 12.5mg 1x1/day).

Physical examination revealed a blood pressure of 130/80 mmHg and a pulse rate of 76 beats/minute that was in rhythm. Her body mass index (BMI) was 49.4 kg/m², and her waist circumference was 135 cm. The secondary reasons for her weight increase were evaluated. Her cortisol value was suppressed (<1.8 microg/dl) after a low-dose dexamethasone suppression test, and her thyroid function tests were normal. Other laboratory results were as follows: fasting plasma glucose: 140 mg/dl, two-hour postprandial plasma glucose: 188 mg/dl, glycated hemoglobin (HbA1c) value: 6.8%, serum urea: 39 mg/dl, serum creatinine: 0.93 mg/dl, serum triglyceride: 219 mg/dl, low-density lipoprotein (LDL): 128 mg/dl, and high-density lipoprotein (HDL): 33 mg/dl. Additionally, her liver function tests and complete blood count were normal. In nephropathy-related investigations, it was seen that her 24-hour urine albumin level was 22 mg/day, and the creatinine clearance was 158 ml/min. The patient, who had stage IV gonarthrosis, had poor exercise compliance. Her diet was analyzed, and in order to promote weight loss, sitagliptin was discontinued, and exenatide [5 mg 2x1 subcutaneously (sc)] was added to her current therapy. On the fifth day of treatment, nateglinide therapy was discontinued because the two-hour postprandial glucose levels were found to be between 70 and 80 mg/dl. After a month of treatment, there was weight loss of 4 kg, and the patient's glycemic targets were reached. She experienced mild nausea at the beginning, but she tolerated the drug, thus, the exenatide dose was increased to 10 mcg 2x1/day.

The patient was admitted to the emergency ward 20 days after the dose enhancement for abdominal pain, nausea, and vomiting. On physical examination, there was widespread tenderness and defense but no rebound. The patient had normal serum amylase and lipase values along with normal liver and renal function tests. Her random plasma glucose level was 110 mg/dl. The abdominal ultrasonography (USG) of the patient, who had been evaluated via general surgery, was found to be within normal limits. Since she had severe pain, and there was widespread tenderness in the abdomen, a contrast-enhanced abdominal computed tomography (CT) was performed. The results were normal, and no sign of acute

pancreatitis was observed. The exenatide was then discontinued because of severe nausea and vomiting. Three days after the discontinuation of this therapy, the symptoms of the patient had subsided, and she was referred to the outpatient clinic. However, the patient insisted that she wanted to restart her therapy since she had lost 8 kg in 50 days under the exenatide therapy. The serum urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), amylase, and lipase levels were normal, thus, exenatide therapy (10 mcg 2x1/day) was restarted.

After one week, the patient was referred to the clinic with complaints of lethargy, nausea, vomiting, and low urine output (200-300 cc per day). Her blood pressure was 90/60 mm Hg, and her pulse was 110 beats/minute. Her tongue was dry, skin turgor and tonus were decreased, and her overall condition was only average. Her body weight was 88 kg, and it was calculated that she had lost another 4 kg in the week since exenatide was restarted. Her laboratory findings revealed the following: serum urea: 88 mg/dl, serum creatinine: 9.47 mg/dl, serum sodium: 140 mmol/l, serum potassium: 4.6 mmol/l, creatinine kinase: 53 U/L (N: 29-168), and serum calcium: 9.5mg/dl. The patient's urine density was 1023, serum osmolality was 630 mOsm, and pH was 5. There were 4-5 leukocytes and 5 erythrocytes in the urine microscopy along with inactive urine sediment. Renal USG revealed normal renal sizes, paranchyme thickness, and paranchyme echogenicity. Her decrease in oral intake was accompanied by vomiting and, signs of dehydration were observed; hence, parenteral hydration was started. Normal levels of urinary output were achieved during urinary catheterization, which resulted in a return to normal serum creatinine levels (Table). During this period, her plasma glucose levels varied between 90 and 130 mg/dl without treatment. Currently, the patient is being monitored and is undergoing metformin therapy (2g/day), which began two months ago.

Discussion

Exenatide is not a known nephrotoxic agent (5), but it is contraindicated in patients with severe renal failure. In cases of moderate renal failure (creatinine clearance 30-50 ml/min), an attentive increase in the dosage is recommended (8). The United States Food and Drug Administration (FDA) warning in 2009 for possible renal dysfunction with exenatide was based on a review of 78 cases of altered kidney function reported in patients with diabetes between April 2005 and October 2008. It was determined that 79% of cases had ARF. Furthermore, at least 95% of patients in their review were reported to carry at least one risk factor for diminished renal function, such as nephrotoxic drug use, heart failure, or hypertension (9).

Weise et al. (4) reported deterioration in renal functions of four patients who were on exenatide therapy, with all four experiencing nausea and vomiting. Incomplete healing was seen in three of the patients after treatment with exenatide was discontinued. In a study by Nandokoban et al. (6), ARF occurred in a patient due to acute tubulointerstitial nephritis that had developed after treatment with exenatide, and this was confirmed by a renal biopsy. Bhatti et al. (10) reported deterioration in renal functions in two patients following

Tablo 1. Serum urea and creatinine levels

	Serum urea (mg/dl)	Serum Cr (mg/dl)
DAY 0	88	9.47
DAY 1	85	8.56
DAY 2	72	5.07
DAY 3	52	2.16
DAY 4	35	1.38
DAY 5	30	0.95
DAY 10	25	0.9
DAY 60	33	0.72

exenatide therapy. Dehydration was present in one of these patients, and that patient's renal functions was reported to have improved by hydration. The other patient did not have dehydration and had no response to hydration treatment. A diagnosis of interstitial nephritis was suspected and prednisolone therapy was started, which resulted in incomplete healing of the patient's renal functions. Lopez-Ruiz et al. (5) reported an ischemic acute ARF due to severe intolerance (constant nausea, vomiting, and dehydration) in the second month of exenatide treatment. It was suggested that angiotensin II receptor blockers (ARBs) and the use of a diuretic have had triggered the serious adverse reaction.

Exenatide is used in patients at risk for renovascular disease, and it is frequently associated with potentially nephrotoxic drugs such as metformin, angiotensin-converting enzyme (ACE) inhibitors, ARBs, and diuretics. Moreover, exenatide may lead to ischemic renal failure because of hypovolemia and dehydration in cases in which patients do not have adequate liquid intake and, therefore, suffer from nausea and vomiting related to the therapy (8). Except for various case reports and the FDA warnings, only one study that has assessed the relationship between the use of exenatide and ARF has failed to find a significant relationship. However, the authors of that study stated that they could not overlook a minimal increase of risk (7).

In our case, there was dehydration that accompanied severe nausea and vomiting. With hydration, there was improvement in the patient's renal functions. Other risk factors, including a history of hypertension, ARF, diuretic use, and exposure to radiocontrast medium were present as well.

Contrast medium-induced nephropathy is described as a 25% or a 0.5 mg/dl increase in the basal serum creatinine level observed 48 hours after exposure to the contrast medium. These levels reach their peak after the second and third day and then decline (11). In our patient, renal function tests were found to be within normal limits 72 hours after radiocontrast medium intake, thus, excluding the

possibility of contrast medium-induced nephropathy. As a result, ARF in our case was thought to result from hypovolemia related to the vomiting and limited oral intake of the patient.

ARF is not a common adverse effect encountered following the use of exenatide. However, since the number of case reports is increasing, it is understood that physicians should be alert for ARF in patients taking this medication. In conclusion, renal functions should be closely monitored, especially for patients prescribed nephrotoxic agents and for those with a high risk of nephropathy and dehydration due to their treatment with exenatide. The dosage of this drug should be also be carefully planned.

References

1. Drucker DJ, Sherman SI, Gorelick FS, et al. Incretin-based therapies for the treatment of type 2 diabetes: evaluation of the risks and benefits. *Diabetes Care* 2010;33:428-33.
2. Kendall DM, Cuddihy RM, Bergenstal RM. Clinical application of incretin-based therapy: therapeutic potential, patient selection and clinical use. *Eur J Intern Med* 2009;20(Suppl 2):329-39.
3. Kim D, MacConnell L, Zhuang D, et al. Effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and body weight in subjects with type 2 diabetes. *Diabetes Care* 2007;30:1487-93.
4. Weise WJ, Sivanandy MS, Block CA, Comi RJ. Exenatide-associated ischemic renal failure. *Diabetes Care* 2009;32:22-3.
5. López-Ruiz A, del Peso-Gilsanz C, Meoro-Avilés A, et al. Acute renal failure when exenatide is co-administered with diuretics and angiotensin II blockers. *Pharm World Sci* 2010;32:559-61.
6. Nandakoban H, Furlong TJ, Flack JR. Acute tubulointerstitial nephritis following treatment with exenatide. *Diabet Med* 2013;30:123-5.
7. Pendergrass M, Fenton C, Haffner SM, Chen W. Exenatide and sitagliptin are not associated with increased risk of acute renal failure: a retrospective claims analysis. *Diabetes Obes Metab* 2012;14:596-600.
8. Ferrer-García JC, Martínez-Chanza N, Tolosa-Torréns M, Sánchez-Juan C. Exenatide and renal failure. *Diabet Med* 2010;27:728-9.
9. Available from URL: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm188703.htm>. Accessed 5 June 2010.
10. Bhatti R. Exenatide associated renal failure. *Pract Diabetes Int* 2010;27:3.
11. Aspelin P, Aubry P, Fransson SG, et al. Nephrotoxic effects in high-risk patients undergoing angiography. *N Eng J Med* 2003;348:491-9.